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New Reactions of Benzocaine

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Abstract—Reaction of benzocaine with indane-1,3-dione-2-carbaldehyde afforded the corresponding azomethine. Ethoxymethylenemalonate reacted with benzocaine to form ethyl 4-{[2-(ethoxycarbonyl)-4-methoxy-3-oxobuten-1-yl]amino}benzoate, which was converted to the corresponding quinolone when heated to 185–190°C. Reactions of benzocaine with aliphatic aldehydes furnished 2,3-alkyl-substituted quinolines.

Keywords: aromatic amines, benzocaine, quinolones, 2,3-substituted quinolines

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Aromatic amine derivatives are suitable starting materials for the synthesis of various biologically active derivatives of quinoline. A number of 8-hydroxyquinoline derivatives possess antibacterial, antiparasitic and antifungal activity [1]. Gould–Jacobs reaction, Combes and Skraup quinoline syntheses are general methods of preparation of substituted quinolines starting from aromatic amines. 6,7-Difluoro-substituted quinolones (precursors in the synthesis of fluoroquinolone antibiotics) are known to be produced by reacting 3,4-difluoroaniline with ethoxymethylene-malonate [2]. 2,3-Alkyl-substituted quinolines can be obtained by reacting aliphatic aldehydes with aniline in the presence of $LnCl_3 \cdot 6H_2O$ [3]. Benzocaine (ethyl *p*-aminobenzoate), which is an active local anesthetic agent, is prepared by reducing ethyl *p*-nitrobenzoate. Previously, we have suggested an efficient method of catalytic reduction of ethyl *p*-nitrobenzoate [4]. In turn, benzocaine is the starting material for the synthesis of β-diethylaminoethyl *p*-aminobenzoate hydrochloride (Procaine drug) [5].

Since benzocaine is an industrial product, it was appropriate to use this available aromatic amine derivative as a starting material for a synthesis of new compounds with potential biological activity. In this regard, the aim of the present work was to develop new synthetic approaches and to use the known methods for obtaining new *p*-aminobenzoic acid derivatives and fused benzopyridines (quinolines).

We found that the reaction of benzocaine **1** with indane-1,3-dione-2-carbaldehyde **2** in ethanol resulted in the formation of ethyl 4-{[(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methylene]amino}benzoate **3** (Scheme 1).

In the ^{1}H NMR spectrum of compound **3** a spin-spin coupling between of the signals of methine protons and amino group is registered that indicates the existence of an enamine tautomer **3a** (Scheme 2).

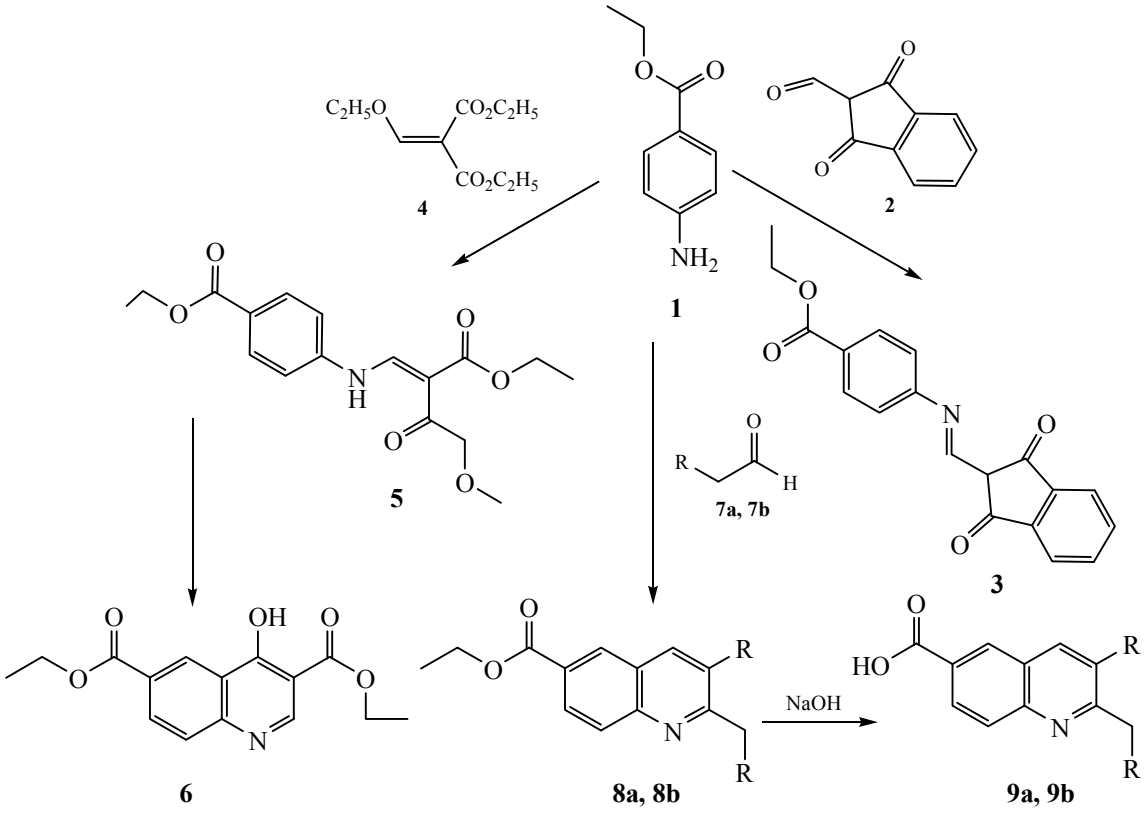
The reaction of benzocaine **1** with ethoxymethylene-malonate **4** proceeded smoothly in a formic acid solution at 50–55°C to give ethyl 4-{[2- (ethoxycarbonyl)-4-methoxy-3-oxobuten-1-yl]amino}benzoate **5**. According to NMR data, in dimethylsulfoxide solution compound **5** is an enamine isomer.

Upon heating at 185–190°C in dodecane, benzoate **5** underwent cyclization to form quinoline **6** (Scheme 1), which is capable of keto-enol tautomerism. The lack of spin-spin interactions between the protons of adjacent NH and CH groups of heterocycle in the ^{1}H NMR spectrum of compound **6** indicates the existence of enol isomer in dimethylsulfoxide solution.

Reactions of aromatic amines with ethoxymethylene-malonic acid esters leading to the formation of substituted 4-oxyquinolines (quinolones) are known as the Gould–Jacobs reaction [6]. We have performed such conversion of 3,4-difluoroanilines earlier in the synthesis of intermediates for fluoroquinolone antibiotics [2].

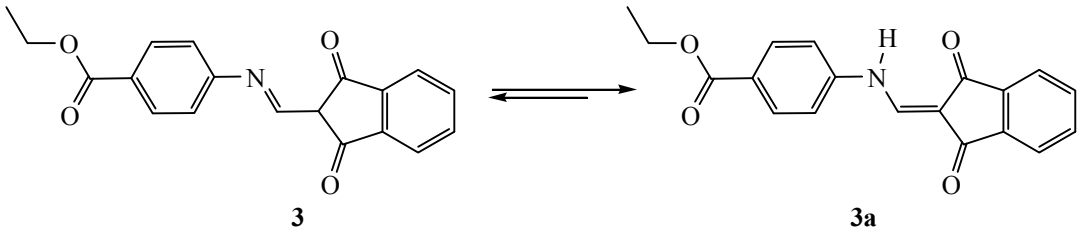
We discovered unusual transformations when reacting benzocaine **1** with aliphatic aldehydes **7a** and **7b** in formic acid. The reaction afforded the corresponding

Scheme 1.



R = Et (**a**), Pr (**b**).

Scheme 2.



3 **3a**

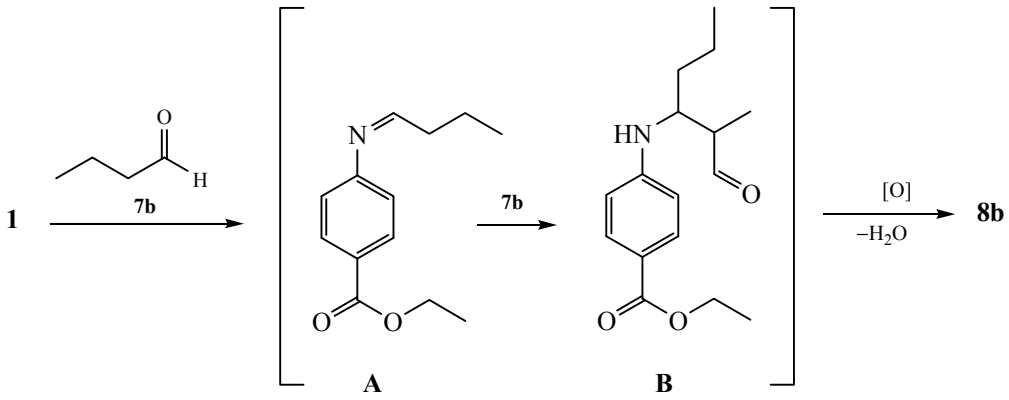
2,3-substituted quinoline derivatives **8a** and **8b** (Scheme 1). The structure of the compounds obtained was confirmed by mass spectrometry and NMR spectroscopy data.

Obviously, the formation of quinolines **8** occurs as a result of the reaction between 1 mol of benzocaine with 2 mol of the corresponding aldehyde. Apparently, the initially formed azomethine **A** adds the second aldehyde molecule; and the resulting intermediate **B** undergoes ring closure to form quinoline **8** (Scheme 3). Brief heating of esters **8** in an aqueous alcohol alkali solution led to the formation of the corresponding acids **9**.

Hence, we have found a new type of transformations in which benzocaine reacts with two molecules of the starting aldehyde that get cross-linked with each other and acting as a 1,3-dicarbonyl reagent. As a result, it makes possible to obtain 2,3-alkyl-substituted quinolines in one step in the reaction of benzocaine with aliphatic monocarbonyl compounds.

In conclusion, it should be noted that the obtained new quinoline and benzocaine derivatives are not only of interest as potentially active compounds, but may also be used as synthons, which may be modified due to the presence of carboethoxy moiety in an aromatic or heterocyclic core.

Scheme 3.



EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer. Electron impact mass spectrometry was performed on a GCMS-QP2010 Ultra Shimadzu instrument (Japan) at 75 eV and 200°C.

Ethyl 4-{[(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-methylene]amino}benzoate (3). To a solution of 0.082 g (0.5 mmol) of benzocaine **1** in 5.0 mL of ethanol 0.087 g (0.5 mmol) of aldehyde **2** was added. The mixture was stirred for 10–15 min. After cooling the precipitate was filtered off, washed with water and 2.0–3.0 mL of ethanol, and then dried. Yield 0.106 g (66.0%), mp 234–235°C (DMF). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.43 t (3H, CH_3, J = 7.2 Hz), 4.40 q (2H, CH_2, J = 7.2 Hz), 7.28 d (2H, CH_{Ar}, J = 5.6 Hz), 7.30–7.75 m (2H, CH_{Ar}), 7.82–7.88 m (2H, CH_{Ar}), 8.12 d (2H, CH_{Ar}, J = 5.6 Hz), 8.26 d (1H, N=CH, J = 13.6 Hz), 10.98 d (1H, NH, J = 13.6 Hz). Mass spectrum, m/z (I_{rel}, %): 321 (100) $[M]^+$. Found, %: C 71.13; H 4.65; N 4.53. $C_{19}H_{15}NO_4$. Calculated, %: C 71.02; H 4.71; N 4.36.

Ethyl 4-{[(2-(ethoxycarbonyl)-4-methoxy-3-oxo-buten-1-yl]amino}benzoate (5). A mixture of 0.25 g (1.5 mmol) of benzocaine **1**, 1.0 g (4.5 mol) of ethoxymethylenemalonate **4**, and 5.0 mL of formic acid was stirred at 50–55°C for 5–6 h. The solvent was removed, and the precipitate was treated with 3.0–5.0 mL of ethanol. Next, the precipitate was filtered off and dried. Yield 0.240 g (50.0%), mp 72–73°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 t (3H, CH_3, J = 7.2 Hz), 1.34 t (3H, CH_3, J = 6.8 Hz), 1.38 t (3H, CH_3, J = 7.2 Hz), 4.17 q (2H, CH_2, J = 6.8 Hz), 4.25 q (2H, CH_2, J = 7.2 Hz), 4.32 q (2H, CH_2, J = 7.2 Hz), 7.39 d (2H, CH_{2Ar}, J = 8.8 Hz), 7.97 d (2H, CH_{2Ar}, J = 8.4 Hz), 8.45 d (1H, CH, J = 13.2 Hz), 10.86 d (1H, NH, J = 13.2 Hz). Mass spectrum, m/z (I_{rel}, %): 335 (90) $[M]^+$. Found, %: C 60.65; H 6.52; N 4.05. $C_{17}H_{21}NO_6$. Calculated, %: C 60.89; H 6.31; N 4.18.

Diethyl 4-oxyquinoline-3,6-dicarboxylate (6). A solution of 0.335 g (1.0 mmol) of **5** in 5 mL of dodecane was heated at 185–190°C for 1 h. The precipitate was filtered off, washed with 2.0 mL of ethanol, and dried. Yield 0.2 g (70.0%), mp >250°C (aq. DMF). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 t (3H, CH_3, J = 6.8 Hz), 1.43 t (3H, CH_3, J = 6.8 Hz), 4.27 q (2H, CH_2, J = 6.8 Hz), 4.39 q (2H, CH_2, J = 6.8 Hz), 7.66 d (1H, CH_{Ar}, J = 8.8 Hz), 8.15 d. d (1H, CH_{Ar}, J = 8.8, J = 2.0 Hz), 8.52 s (1H, CH_{Ar}), 8.76 d (1H, CH_{Ar}, J = 2.0 Hz), 12.36 s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 289 (88) $[M]^+$. Found, %: C 62.52; H 5.34; N 4.69. $C_{15}H_{15}NO_5$. Calculated, %: C 62.28; H 5.23; N 4.84.

Ethyl 2-propyl-3-ethylquinoline-6-carboxylate (8a). A mixture of 0.5 g (3.0 mmol) of benzocaine **1** and 1.0 g (13.9 mmol) of butanal in 5.0 mL of formic acid was stirred at 50–55°C for 5 h. After the solvent was removed the residue was treated with 5.0 mL of ethanol. The precipitate was filtered off and recrystallized from ethanol. Yield 0.300 g (36.0%), mp 91–92°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.05 t (3H, CH_3, J = 7.2 Hz), 1.36 t (3H, CH_3, J = 7.6 Hz), 1.44 t (3H, CH_3, J = 7.2 Hz), 1.82–1.93 m (2H, CH_2), 2.85 q (2H, CH_2, J = 7.6 Hz), 2.94 t (2H, CH_2, J = 7.6 Hz), 4.39 q (2H, CH_2, J = 7.2 Hz), 7.93 d (1H, CH_{Ar}, J = 8.8 Hz), 8.10 s (1H, CH), 8.11 d. d (1H, CH_{Ar}, J = 8.0, J = 2.0 Hz), 8.51 d (1H, CH_{Ar}, J = 2.0 Hz). Mass spectrum, m/z (I_{rel}, %): 271 (20) $[M]^+$. Found, %: C 75.62; H 7.98; N 5.03. $C_{17}H_{21}NO_2$. Calculated, %: C 75.25; H 7.80; N 5.16.

Ethyl 2-butyl-3-propylquinoline-6-carboxylate (8b) was prepared similarly from 0.5 g (3.0 mmol) of benzocaine **1** and 1.0 g (11.6 mmol) of pentanal. Yield 0.35 g (38.0%), mp 77–78°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 t (3H, CH_3, J = 7.2 Hz), 1.08 t (3H, CH_3, J = 7.2 Hz), 1.46 t (3H, CH_3, J = 7.2 Hz), 1.52–1.56 m (2H, CH_2), 1.70–1.90 m (4H, CH_2), 2.81 t (2H, CH_2, J = 8.0 Hz), 3.02 t (2H, CH_2, J = 8.0 Hz), 4.45 q (2H, CH_2, J = 7.2 Hz), 7.95 s (1H, CH), 8.05 d (1H, CH_{Ar}, J = 8.8 Hz), 8.22 d. d (1H, CH_{Ar}, J = 8.8, J = 1.6 Hz), 8.51 d (1H, CH_{Ar}, J = 1.6 Hz). Mass spectrum, m/z (I_{rel}, %): 299 (10) $[M]^+$. Found, %: C 76.53; H 8.60; N 4.51. $C_{19}H_{25}NO_2$. Calculated, %: C 76.22; H 8.42; N 4.68.

2-Propyl-3-ethylquinoline-6-carboxylic acid (9a). A mixture of 0.13 g (0.53 mmol) of **8a**, 0.130 g (3.2 mmol) of NaOH and 10 mL of 50% ethanol was refluxed for 25–30 min, and then treated with 15% HCl (pH 3–4). The precipitate was filtered off and recrystallized from aqueous ethanol. Yield 0.090 g (77.0%), mp 180–181°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.05 t (3H, CH_3, J = 7.6 Hz), 1.34 t (3H, CH_3, J = 7.6 Hz), 1.81–1.90 m (2H, CH_2, J = 8.0 Hz), 2.81–2.95 m (4H, CH_2), 7.90 d (1H, CH_{Ar}, J = 8.4 Hz), 8.10–8.07 m (2H, CH_{Ar}), 8.49 d (1H, CH_{Ar}, J = 2.0 Hz), 12.82 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 243 (35) $[M]^+$. Found, %: C 74.36; H 7.23; N 5.99. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.76.

2-Butyl-3-propylquinoline-6-carboxylic acid (9b) was prepared similarly. Yield 65.0%, mp 131–132°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 t (3H, CH_3, J = 7.6 Hz), 1.06 t (3H, CH_3, J = 7.6 Hz), 1.46–1.51 m (2H, CH_2), 1.69–1.84 m (4H, CH_2), 2.79 t (2H, CH_2, J = 7.6 Hz), 2.95 t (2H, CH_2, J = 7.6 Hz), 7.91 d (1H, CH_{Ar}, J = 8.8 Hz), 8.07–8.11 m (2H, CH_{Ar}), 8.47 d (1H, CH_{Ar}, J = 1.6 Hz), 12.77 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 271 (10) $[M]^+$. Found, %: C 75.36; H 7.82; N 5.34. $C_{17}H_{21}NO_2$. Calculated, %: C 75.25; H 7.80; N 5.16.

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